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Big Data Approaches for Modeling Response and Resistance to Cancer Drugs

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Abstract
Despite significant progress in cancer research, current standard-of-care drugs fail to cure many types of cancers. Hence, there is an urgent need to identify better predictive biomarkers and treatment regimes. Conventionally, insights from hypothesis-driven studies are the primary force for cancer biology and therapeutic discoveries. Recently, the rapid growth of big data resources, catalyzed by breakthroughs in high-throughput technologies, has resulted in a paradigm shift in cancer therapeutic research. The combination of computational methods and genomics data has led to several successful clinical applications. In this review, we focus on recent advances in data-driven methods to model anticancer drug efficacy, and we present the challenges and opportunities for data science in cancer therapeutic research.
INTRODUCTION
Although oncologists started testing chemotherapy in patients during the 1940s, cancer remains one of the deadliest diseases in developed countries after eighty years. Research directed at understanding tumorigenesis and developing effective therapies has yielded significant successes. For example, the introduction of all-\textit{trans} retinoic acid (ATRA) to treat acute promyelocytic leukemia driven by \textit{RAR}$\alpha$ translocation led to a cure in most patients suffering from this previously deadly disease (1). The use of imatinib in treating chronic myelogenous leukemia driven by the \textit{BCR-ABL} fusion resulted in an $\sim$80% decline in disease mortality (2). However, the success of ATRA, imatinib, and others including \textit{EGFR} and \textit{ALK} inhibitors (3, 4) in substantially improving long-term survival has been the exception rather than the norm. Currently, most tumors, once metastatic, remain incurable (5). Many targeted cancer drugs such as inhibitors of \textit{AKT} and \textit{IGF1R}, which show significant effects in preclinical models, fail to bring sufficient clinical benefits (6, 7). Many anticancer drugs also have debilitating side effects, and lowering the dose to control side effects can significantly limit therapy effectiveness (8, 9). Even with the significant progress of immunotherapies in recent years, only a minority of patients with specific cancer types benefit from the immune checkpoint blockade (ICB), and many patients relapse during ICB therapy (10). Therefore, there remains a significant unmet need for the scientific community to develop better anticancer treatments and predict patient responses.

Conventionally, hypothesis-driven studies are the driving force of cancer therapeutic discoveries. Recently, the rapid growth of big data resources has resulted in a paradigm shift (11). The application of omics technologies, from high-throughput sequencing to automated screening (Figure 1a), has generated large-scale data sets that capture different aspects of anticancer drug efficacy (Figure 1b). Computational methods are essential for the analysis of these big data resources (Figure 1c) to generate clinically useful results in predicting therapeutic response and side effects and in designing combination therapies (Figure 1d). Precision cancer medicine aims to understand the tumor microenvironment, host immunity, and the ecosystem at the molecular level to find treatments that best fit more patient subgroups. With fast-growing data and analytical resources, the scientific community is moving toward this goal of precision medicine. In this review, we focus on recent advances in data-driven approaches in modeling anticancer drug response and resistance. We also introduce readers to other reviews that cover the basic science and clinical aspects of anticancer drug response (5, 10, 12–17). The current review, as well as the literature cited within, provide an overview of the challenges and opportunities of data science in precision cancer medicine.

OMICs TECHNOLOGIES FOR MAKING DATA-DRIVEN DISCOVERIES
Omics technologies, especially fast and affordable next-generation sequencing, have resulted in a flood of big data in cancer research. The advances in genomics resources, catalyzed by the rapid technology development, have enabled discoveries on both actionable clinical solutions and therapy resistance mechanisms. In this section, we review several key genomics technologies and the data generated.

Genome-Scale Profiling of Clinical Samples
Several genomics approaches are enabling the molecular characterization of human cancer samples (Figure 1a). At the DNA level, whole-exome sequencing of over $\sim$20,000 human genes can provide a systematic view of genetic alterations in protein-coding regions (18, 19). Alternatively, whole-genome sequencing can identify driver mutations in noncoding regions (e.g., noncoding
RNAs, promoters, enhancers), and structural variations at high resolution (20, 21). In contrast, clinical assays usually target mutations on a panel of a few hundred genes recurrently mutated in cancer (22). At the RNA level, gene expression profiles can be measured with technologies such as microarrays, RNA sequencing (RNA-seq), or NanoString with varying degrees of gene focus. Together with methods to profile micro RNA expression, protein abundance, DNA methylation,
and chromatin accessibility, these technologies have been applied to patient samples to generate large-scale cancer genomic and epigenomic data. For example, the Cancer Genome Atlas (TCGA) project generated 2.5 petabytes of genome-scale profiling data for cancer and matched normal tissues from more than 11,000 patients across 33 cancer types (23). Another example is the GENIE (genomics evidence neoplasia information exchange) project that released mutation profiles for more than 500 genes and a minimal set of clinical information for almost 30,000 cancer patients until the end of 2017 (24). Such data from many patients with diverse cancer types can inform the treatment decisions of other patients with similar mutations.

To model the mechanisms of intrinsic and acquired resistance to anticancer drugs (5), we need distinct experimental designs. For intrinsic resistance mechanisms, the gene expression or mutation profiles from pretreatment tumors of responders and nonresponders can be compared, while for acquired resistance mechanisms, recurrent genomic and transcriptomic alterations could be identified by comparing post- and pretreatment tumors. For example, a comprehensive study generated whole-exome sequences for 67 triplets of pretreatment tumors, post-treatment tumors, and normal tissues from melanoma patients treated with MAPK inhibitors (25). This study also generated the expression profiles of 48 pairs of pre- and post-treatment (drug-resistant) tumors. For a subset of these tumors, progression-free survival (PFS) data of the patients were available. The pretreatment tumor profiles and PFS information could be used to implicate molecular alterations associated with intrinsic resistance to MAPK inhibitors, while post-treatment profiles could reveal somatic mutation and gene expression drivers of acquired resistance to MAPK inhibitors. This study identified several transcriptomic alterations, such as MET, YAP1, and LEF1 dysregulation, as indicators of acquired resistance to MAPK inhibitors. Meanwhile, the drug-resistant tumors recurrently lose CD8 T cell numbers and cancer cell antigen presentation (25).

### High-Throughput Screening on Preclinical Models

The study of anticancer therapy efficacy would ideally include both tumor molecular profiles and drug response information across a large cohort of patients. However, the expense and effort of collecting such data have limited the number of examples where this has been done. A research alternative to clinical profiling is to use preclinical models, such as immortalized cell lines.
Compound screening in cancer cell lines. Automation frameworks can be utilized to test the growth inhibition effects of a library of compounds across many cancer cell lines with diverse genetic backgrounds. Most compound screen projects also profiled the molecular features (e.g., gene expression, copy number, mutation status) of cell lines. The final data output is the growth inhibition effects of compounds on cell lines, together with cell line molecular profiles.

Supplemental Material
Recently, data on three large-scale compound-screen projects became publicly available. The Cancer Cell Line Encyclopedia (CCLE) (29) project is a collaboration between the Broad Institute and Novartis Institutes for Biomedical Research (NIBR) (30). The investigators collected ∼1,000 human cancer cell lines and completed the acquisition of comprehensive molecular profiling data, including gene expression, copy number alteration, and somatic mutation. The CCLE released the growth inhibition profiles of 24 anticancer drugs across 504 cell lines (29). The Broad and NIBR also independently released gene essentiality measurements, defined as the impact of gene loss on cell growth, on CCLE cell lines through CRISPR and short hairpin RNA (shRNA) screens (31–34). The CCLE screens reported that AHR expression determines MEK inhibitor efficacy in NRAS-mutant lines, and SLFN11 expression predicts sensitivity to topoisomerase inhibitors.

Similar to the CCLE project, the Cancer Therapeutics Response Portal (CTRP) screened more than 500 compounds and their combinations on the CCLE cell lines (35). The Genomics of Drug Sensitivity in Cancer (GDSC) project profiled the sensitivity of about 1,000 COSMIC cell lines to 250 compounds and identified many genetic alterations associated with drug efficacy (36).

Even with automation, large-scale cellular compound screens are labor intensive and expensive. To overcome this challenge, researchers developed a technique called PRISM to perform pooled screens on barcoded cell line mixtures (37). The Luminex microspheres could detect the different growth rates of cell lines under the treatment of either a test compound or a DMSO control by quantifying their barcode fractions in pools (38–40). The difference in the barcode fraction between the treatment and control conditions reflects the inhibition effect of a compound on a given cell line. PRISM was used to screen a large set of compounds in ∼100 cancer cell lines and was extended to screening erlotinib sensitivity in 23 lung cancer cell lines in mouse xenografts (37).

A potential limitation is that the interactions among different cell lines in a pool may confound the drug sensitivity measurements, so the utility of PRISM awaits further evaluation.

A limitation of compound screens is that cultured cell line models cannot reflect the tumor microenvironment (41). Many anticancer drugs not only exert cytotoxic effects but also induce immunological responses (12). Moreover, the effects of antibody drugs, such as trastuzumab, depend on the antibody-dependent cell-mediated cytotoxicity effects from natural killer cells (42). Therefore, numerous murine models were developed to better approximate human tumors. One model is the xenotransplantation of human tumors (xenografts) in immunocompromised mice, in which human tumor cells are transplanted either ectopically under the skin or orthotopically into the organs where the tumor originated. One study established ∼1,000 patient-derived tumor xenograft (PDX) models with a diverse set of driver mutations (43). With these PDX models, the authors performed in vivo screens to assess the responses to 62 compounds with about 2,000 drug response measurements. Many conclusions from this study regarding the factors influencing targeted therapy efficacy are highly consistent with the results from human clinical trials. This PDX screen also provided further validation for both gene mutation and expression biomarkers generated from cell line studies. Moreover, the PDX platform demonstrated the ability to evaluate the clinical efficacy of combination therapies, which may not be faithfully reflected in in vitro assays.

A limitation of the PDX model is that immunocompromised mice cannot simulate the immune response, a critical factor of anticancer drug response (12, 44). Also, there are numerous instances where murine and human ligands and receptors do not cross-signal (45). Genetically engineered and syngeneic recipient mice could help in both of these areas. They would preserve a competent immune system, although compound screens on murine models cannot scale up due to the lack of automation frameworks. Also, it is not yet clear how to create murine models in which the complexity of the genetics of human cancers is modeled more robustly.

A further assessment of immune-active agents can be conducted using the cytotoxic T cell killing assay that could both simulate the effect of immune systems and scale up with robotics.
In this assay, cancer cells with a specific antigen are cocultured with the cytotoxic T cells with the corresponding T cell receptor (46–48). Automated image analysis measures cancer cell death in the presence of both lymphocytes and a candidate compound. A recent study screened 850 compounds for synergistic drugs of T cell–mediated killing using two patient-derived melanoma cell lines and their autologous T cells (47). In principle, the automation frameworks for the cellular compound screens (e.g., CCLE, CTRP, GDSC) could adapt to the format of coculture assays to study the effects of compounds on cancer cells in the presence of a simplified immune system.

Moving from the Bulk Tumor to Single Cells

Most previous studies profiled the cancer genome from bulk tumor tissues, which will give the mixture profiles of cancer, stromal, and immune cells in the tumors. However, the acquisition of drug resistance during the treatment may depend on variations in rare populations (49). Moreover, cell composition, location, and interactions within each tumor play critical roles in determining therapy response (50, 51). For example, patient survival in colorectal cancer depends on the location and density of T cells in the cores and margins of tumors (52). In murine models of breast cancer, the relative spatial distribution in the tumors of M2 macrophage and cancer cells of different phenotypes can explain the tumor immune evasion and immunotherapy resistance (53). Therefore, the conventional technologies of bulk tumor profiling may not be adequate to resolve the heterogeneity and complexity of cancer therapy response.

The past few years have seen the rapid development of single-cell technologies for investigating the cellular heterogeneity in DNA (54), RNA (55), proteins (56), and metabolites (57). For example, a recent study generated the single-cell gene expression profiles in temporal specimens of ovarian cancer patients with acquired platinum resistance (58). This study observed an accumulation of genetically identical cells with distinct transcriptome states, indicating epigenetic mechanisms of treatment resistance. In another study with almost 5,000 single-cell RNA-seq profiles from 19 melanoma patients, investigators found that all tumors harbored cancer cells in a drug-resistant state, indicating the eventual tumor progression to resistance during treatment (59). Recently, a large-scale study profiled the transcriptomes of ~6,000 single cells from 18 head and neck cancer patients and identified a subset of cancer cells enriched with a partial signature of epithelial-to-mesenchymal transition (p-EMT) (60). These cells localized to the leading edge of tumors, where the interactions between cancer-associated fibroblast and malignant cells may promote the p-EMT program and induce tumor invasion. All the studies mentioned above demonstrated the new insights that single-cell technology can bring compared to the conventional bulk tumor profiling.

Both the number and quality of single-cell data sets have significantly increased recently. However, the gene dropout rate, the heterogeneity of populations, and the lack of spatial-temporal context present significant challenges to single-cell genomics (61). Integrative analysis of single-cell and bulk tumor data and cell signatures from previous studies may ameliorate some limitations of single-cell data (59, 62). Meanwhile, single-cell imaging technologies may provide spatial information for different cells and genes in a tumor (63). We foresee that the development of single-cell technologies will rapidly generate rich data sets for understanding the complexity and heterogeneity of cancer drug response and will provide many new opportunities for computational method development.

Extending from Tumor Microenvironment to Host Microbiota

Recently, it has been reported that human microbiota, especially the gut microbiota, modulates the response and side effects from chemotherapies to immunotherapies (17). The human microbiota
is the ensemble of bacteria and other microorganisms that inhabit the epithelial barrier surfaces. Several studies in mice demonstrated that the murine gut microbiota regulates the response to different chemotherapies (64–66). For example, the efficacy of cyclophosphamide (CTX) relies on intestinal bacteria (64, 65). CTX treatment can damage the gut mucus layer, allowing bacteria to penetrate the lamina barrier and translocate to secondary lymphoid organs. Translocated bacteria, such as *Enterococcus hirae* or *Barnesiella intestinihominis*, may activate the innate and adaptive immune cells and initiate antitumor immunity. Recently, several studies have shown that the gut microbiome may significantly influence response to ICB targeting the CTLA4 and PD1/PDL1 proteins (67–71). Moreover, favorable gut microbiota from ICB-responding patients can enhance the antitumor immunity when transplanted into the gut of mice, highlighting the potential value of fecal transplantation (69, 70).

Gut microbiota is a key modulator not only of therapy response but also of drug toxicity. For example, one of the side effects of irinotecan is the intestinal toxicity (severe diarrhea, weight loss, and anorexia) resulting from gut microbiota metabolism. Irinotecan is transformed into its active form, SN-38, in the liver and small intestine and then detoxified in the liver into inactive SN-38-G before being secreted into the gut. Gut bacterial β-glucuronidases can reconvert SN-38-G into active SN-38, which induces significant intestinal toxicity and diarrhea (72).

Two standard approaches for microbiome profiling include high-throughput sequencing of either the whole-metagenome or the genomic DNA sequences of 16S ribosomal RNA genes in the microbe population (73). Whole-metagenome shotgun sequencing provides species-level resolution of bacteria, and with adequate sequencing depth, can quantify the near-complete genomic content of the collection of microbes in a sample. 16S ribosomal RNA sequencing is a cheaper alternative for studying phylogeny and taxonomy of microbes in a sample. In addition to direct microbiome sequencing, computational methods can also infer microbiome compositions by identifying nonhuman nucleic acids from sequencing data of human samples (74–76).

Characterizing specific bacteria strains and understanding their functions might offer insights leading to the discovery of novel therapeutics. For example, metagenomic profiling of bacteria strains in the fecal samples of patients with favorable therapy outcomes identified bacteria strains that enhanced the efficacy of ICB in mice (69, 70). Another example is that identification of microbial sequences in colon cancer RNA-seq data found *Fusobacterium* to be associated with distant metastases of tumors (77). Moreover, antibiotic treatment in PDX models can decrease both *Fusobacterium* load and cancer cell proliferation. Therefore, profiling and targeting the microbiota in response to cancer therapies may become one of the next frontiers of cancer precision medicine.

**COMPUTATIONAL METHODS FOR MODELING DRUG EFFICACY**

The selection of computational methods is a critical step in transforming genomic data into biological insight and clinical application (Figure 1c). The choice of data analysis methods depends on many factors, such as the quality, complexity, and sample size of a data set. Most studies of anticancer drug efficacy involve the variable selection among many gene expression or mutation features, with drug response as the outcome on a limited number of samples. Also, mathematical and network models can help understand the quantitative properties and potential biological mechanisms of drug response and resistance. In this section, we introduce some commonly used computational methods and models for cancer therapeutic discoveries.

**Modeling Associations in Cancer Genomics Data**

In many studies, a common practice is to primarily model the linear relationships between gene features and drug efficacy outcomes (Figure 3a, left panel). For example, most cancer biomarker
studies explored whether the somatic mutation status or expression level of a gene set can predict therapy outcomes (78). Such problems can be solved with variable selection methods under a unified framework of linear models (Figure 3b). If drug response is a vector of continuous values across samples, least squares regression can be applied to identify gene mutation or expression features associated with drug efficacy (79). If drug response is a vector of binary responder status, logistic regression can be applied (79). If drug response is a vector of patient survival with censorship to remove patients after a follow-up time, Cox proportional hazard (Cox-PH) regression
can be applied to identify essential features (80). Each regression method has assumptions and requirements on input data; therefore, data preprocessing and a sanity check of results are necessary to ensure analysis reliability (81).

In some cases, the modeling of nonlinear relationships might be critical to inferring gene function in cancer (Figure 3a, middle panel). For example, tumors with high levels of PDL1, a T cell exhaustion driver, resist killing by cytotoxic T cells (82). However, the level of PDL1 expression in melanoma tumors is associated with improved survival, which contradicts the protumor role of PDL1 (Supplemental Table 1, top rows). This counterintuitive association arises from the positive correlation between the level of PDL1 and lymphocyte infiltration in melanoma tumors, and patients with higher lymphocyte infiltration in tumors have longer survival than those with lower infiltration (83). In a Cox-PH regression that models nonlinear relationships, the quadratic term of the PDL1 (variable X) is associated with higher death risk Y (Supplemental Table 1, bottom rows). A significant quadratic term represents a U-shape correlation between a variable X and outcome Y (Figure 3a, middle panel) (81), which associates a higher PDL1 level with worse patient survival among lymphocyte-high tumors with high PDL1 levels.

Another critical variable relationship is the interaction. The concept of statistical interaction between variables is different from physical or genetic interactions between proteins or genes. In statistics, interaction occurs when the association between a variable X and outcome Y depends on the status of another variable T (79). In a hypothetical example (Figure 3a, right panel), variable X could have either a positive or negative correlation with Y when the variable T is 1 or 0, respectively. The variable interaction could be tested by a multiplication term in a multivariate regression (79). In some cases, the interaction between variables, rather than the individual variables, might be predictive of anticancer drug efficacy. For example, we developed a method named CARE (computational analysis of resistance) to model how the drug-targeted gene interacts with other genes to affect drug efficacy in cellular compound screens (84). When evaluated using clinical data of targeted therapies, the CARE signatures of gene variable interactions can predict patient outcomes better than signatures of individual gene effects (84).

### Selecting Variables in High-Dimensional Data

Many clinical data sets in cancer research have small sample sizes (e.g., fewer than 100 patients) but a vast number of features (e.g., the expression or mutation status of 20,000 human genes). This type of data sets is termed high-dimensional. In these settings, classical regression methods will fail, including least squares, logistic, and Cox-PH regressions. Each classical regression method computes an optimal coefficient vector to minimize an objective function that measures the coherence between the model and the training data. However, a unique optimal coefficient vector does not exist in a high-dimensional setting because many sets of coefficients could make the model perfectly fit the training data, even when the variables are completely unrelated to the response (79). Moreover, the fitted models may not have reliable prediction performance on an independent test data set, a problem known as overfitting. Nonetheless, the classical methods can be modified with several techniques to perform variable selection in high-dimensional data (Figure 3c,d).

A popular technique is regularized regression, which optimizes a linear combination of the objective function and convex penalty terms on coefficients (Figure 3c) (85). These penalties help find coefficients of the optimal solution in high-dimensional settings while preventing the regression procedure from overfitting the training data (86). One common penalty, named L1 or LASSO (least absolute shrinkage and selection operator) shrinkage, controls the sum of absolute values of all coefficients (Figure 3c). LASSO regression achieves variable selection by setting most coefficients to zero and leaving the coefficients of essential variables as the only nonzero
coefficients (87). Another common penalty, named L2 or ridge shrinkage, controls the sum of squares of all coefficients (Figure 3c). Although ridge regression assigns nonzero coefficients to most variables and thus does not select variables, it can achieve better prediction performance than LASSO when the variables are highly colinear (85).

Elastic net regression combines the advantage of LASSO and ridge regressions by optimizing the linear combination of the objective function and the two penalties (85). The penalty weights ($\lambda_1$ and $\lambda_2$ in Figure 3c) are those that give the lowest cross-validation error. This regularization method could be applied to least squares, logistic, and Cox-PH regressions. Elastic net is very popular in cancer genomics data analysis. For example, elastic net of least squares regression is used in compound screen projects to select gene features (e.g., mutation, copy number, expression) associated with drug efficacy (29, 88).

Another popular approach in high-dimensional variable selection is the stepwise forward regression (81). This method utilizes a greedy approach to select the current best variable from the candidate pool to minimize the model error in a stepwise manner (Figure 3d). The model error can be computed through cross-validation or statistical metrics such as the Bayesian information criterion (81). At each forward step, some previously selected variables may become insignificant, and a backward removal step may eliminate these variables from the model. Compared to elastic net, forward selection in least squares regression is more computationally efficient through a highly optimized implementation (89). Forward selection and its variations are widely used. For example, the elucidation of the EndoPredict® biomarker, a predictor of disease risk in breast cancer, involved the forward-backward selection to identify gene expression features of disease recurrence (90).

Besides elastic net and forward selection, many other approaches, such as linear support vector machine (91) and random forest (81), are also applicable to high-dimensional data. The consortium of Dialogue on Reverse Engineering Assessment and Methods (DREAM) hosted a challenge that evaluated 44 algorithms on their performance of predicting drug sensitivities in compound cell line screens (92). This DREAM challenge reported several interesting observations. First, all top solutions modeled nonlinear relationships. Second, predictive power benefited from prior knowledge of biological pathways. Third, gene expression data provided the highest predictive power among all data types, and performance could be further improved by including other data types. Fourth, integrating predictions from independent methods produced the most robust results because different methods had complementary advantages in examining different aspects of the data.

What makes high-dimensional variable selection possible is the assumption that most regression coefficients are zero, where nonzero values indicate the essential variables (93). However, the colinearity among variables in biological data often fails to meet these criteria (94). Especially when the number of variables is much higher than the sample size, any variable can be well approximated by a couple of spurious variables due to chance correlation (81, 93). In such cases, we may choose the wrong variables and draw false conclusions. A critical procedure to overcome the colinearity issue is to train the model parameters through cross-validation and to evaluate the quality of fitted models on independent test data. Meanwhile, some prior knowledge may inform the grouping of correlated variables into one. For example, the gene expression values of many immune cell markers are highly correlated in bulk tumor profiles. They could be bundled as one feature (95). Notably, inferring immune infiltration in tumors should be taken with extra caution because gene signatures of different cell types might be highly correlated (96). Other complementary resources may also help us to significantly reduce the data dimensionality by limiting the variable selection on smaller gene subsets. For example, when searching for regulators of drug efficacy in a clinical data set, we could focus on the top hits in genetic screens, where the gene knockdown effects on drug sensitivity are evaluated at genome scale in cancer models.
Applying Systems Biology Models

In addition to variable selection, mathematical models are useful approaches in cancer research because of their ability to explore the quantitative properties of drug response (97). For example, previous work by Norton & Simon that modeled tumor growth patterns found that cancer cell growth may follow an S-shaped curve, where the growth rate is lowest for both small and large tumors but highest at an intermediate tumor size (98). Since some chemotherapies may preferentially kill proliferating cells, a dose capable of depleting a tumor of intermediate size may not be sufficient to cure a small or large tumor due to the growth rate difference. Therefore, chemotherapy might have reduced efficacy if an insufficient dose is administered at a time when the tumor is kinetically less sensitive to treatment. This kinetic resistance is different from the acquired and intrinsic resistance caused by molecular mechanisms. Later, a clinical trial validated the results from Norton & Simon’s mathematical model, finding that intense and prolonged doses are necessary for the clinical efficacy of chemotherapies (99). This example highlighted the utility of mathematical models in guiding therapy delivery schedules (100–102).

Besides mathematical models, biological network models are another class of promising approaches, especially for finding regulators. Often, gene features identified by variable selection methods (discussed above) may be associated only with drug efficacy, but not the regulators. Even though genetics screens, such as CRISPR and shRNA screens, can systematically identify the regulators of drug efficacy in cell line models, these technologies cannot be easily applied to patient tumors. Network models have the advantage of integrating the genomic profiles of patient tumors and inferring the potential regulators and pathways (103–105). A previous study demonstrated that, when integrated with gene expression or histone marks, biological networks are predictive of the regulator genes of cancer cell vulnerability (106). Hypothetically, similar network methods could also be applied to identify regulators of anticancer drug response and resistance. Furthermore, network models can be combined with mathematical models to study the quantitative properties of drug combinations (107) and design synergistic drug combinations (108). Therefore, we foresee system biology models playing a more significant role in finding effective cancer therapies in the future.

TRANSLATION: FROM DATA ANALYTICS TO CLINICAL APPLICATIONS

The development of high-throughput technologies is accelerating the translation of basic cancer research discoveries into clinical practice (Figure 1d). The previous decade has witnessed the translation of several research results from genomics data to FDA-approved or -marketed biomarker tests in the clinic. Meanwhile, many recently developed data-driven approaches have also shown promising potential for clinical application.

Identifying Prognostic Biomarkers

Drug response biomarkers are of critical clinical value because patients who do not benefit from a therapy not only waste time and money but also may suffer severe side effects. Early discoveries of cancer biomarkers mainly depended on biological understanding and empirical observations. With the rapid development of genomics resources, data-driven approaches can be used to identify reliable biomarkers. The classic examples are genomics tests for predicting recurrence risk in early-stage estrogen receptor (ER)/progesterone receptor (PR)-positive, HER2-negative breast cancer patients. Since such patients enjoy good clinical benefit from adjuvant endocrine therapy alone (109), it would be ideal for low-risk patients to avoid the unnecessary side effects of
**Figure 4**

Biomarker training using clinical and cell line data. (a) The training of a multigene biomarker to guide treatment decisions starts from a collection of tumor genomics profiles paired with the patients’ clinical outcomes. The association between gene profiles and patients’ clinical outcomes is tested by statistical models, and a subset of genes are selected through a cross-validation procedure to optimize prediction accuracy. The accuracy of the gene biomarker will be evaluated in clinical trials for Food and Drug Administration approval or commercialization. (b) Computational methods can identify response biomarkers from compound screen data. Statistical methods can identify genes whose molecular status is significantly associated with drug efficacy across screened cell lines. The identified biomarker could be a subset of genes or a genome-wide vector of scores with one value per gene. In the latter case, the therapy response of each patient could be predicted by correlating between tumor gene expression values and biomarker scores.

additional chemotherapy. The earliest genomic biomarker of disease recurrence in breast cancer, the Oncotype DX® assay, was developed by combining prior knowledge and heuristic gene selection (110–112). The development of later biomarkers, such as MammaPrint®, EndoPredict, and Prosigna®, all utilized variable selection methods on clinical data cohorts (Figure 4a).

The authors of MammaPrint conducted a microarray transcriptome profiling of 78 tumors and found that the expression levels of 231 genes were correlated with recurrence risk (113). They finalized a 70-gene biomarker set by sequentially selecting genes from the list ordered by the magnitude of correlation and evaluating the classification accuracy using leave-one-out cross-validation. For each tumor, MammaPrint computes the Pearson correlation between the tumor expression profiles and the average profile from the good prognosis groups to predict recurrence risk using a threshold determined from the training data. The MINDACT trial, which investigated the utility of biomarkers in predicting chemotherapy benefits, confirmed the accuracy of MammaPrint (114).
The training of MammaPrint only used data from one expression cohort. However, the development of most genomics biomarkers usually integrates data from several independent cohorts with hundreds of patients profiled. For example, the training data of the EndoPredict assay comprised both newly collected and published microarray cohorts, which included 964 tumors from patients treated with adjuvant tamoxifen (90). The authors searched for gene probes from microarray platforms with sufficient expression dynamics and selected 104 candidate genes through Cox-PH regression with recurrence as the outcome. Then, a forward-backward feature selection procedure (81) identified genes whose level could significantly predict recurrence risk (Figure 3d). The authors selected the parameters in their model through cross-validation, and the final predictor comprises eleven genes, including eight cancer risk genes and three normalization controls. For each tumor, the EndoPredict assay assigns a risk score using a linear model that combined the expression level of eleven predictor genes and several clinical parameters. Thresholds for the risk score are determined using the training data to discriminate patients into low- and high-risk groups.

The training methods of both MammaPrint and EndoPredict were supervised procedures with disease recurrence status as the outcome. Predictive biomarkers can also come from unsupervised procedures on data sets without clinical outcome data. For example, Prosigna (previously known as PAM50) is a widely used genomic test used to classify breast tumor subtypes (115). The authors collected microarray cohorts from both public domain and in-house collections that included 189 breast tumors and 29 normal samples. Hierarchical clustering of the expression profiles identified clusters representing the intrinsic subtypes (e.g., luminal A, luminal B, HER2, basal, normal). The gene expression profile of a patient’s tumor was compared with each of the pretrained signatures to determine the subtype. In the MA.12 study, the PAM50 classification was superior to immunohistochemistry assay in predicting both overall survival and tamoxifen benefit (116).

There are many other similar biomarkers for predicting disease recurrence risk and therapeutic benefits in ER/PR-positive breast cancer, such as the breast cancer index (117, 118) and Mammostrat® (119). An analysis comparing several expression biomarkers for breast cancer found that despite little gene overlap, the different biomarkers showed significant prediction agreement (120). Similar biomarkers also exist for other cancer types, such as ColoPrint® for colon cancer (122), Decipher® (123), Oncotype Dx for prostate cancer (124), and Pervenio™ for early-stage lung cancer (125).

Despite the rapid advance of predictive biomarkers driven by genomics data, there are still significant challenges. Most current commercial biomarker efforts have focused on diseases with a favorable clinical outcome. For example, among ER/PR-positive breast cancer patients tested by MammaPrint and Oncotype Dx, the five-year disease-free rate without chemotherapy is higher than 90% in the low-risk group as determined by conventional clinical measures (114). Most newly diagnosed prostate cancer cases tested by Oncotype Dx represent low-risk disease, with less than 3% of men dying from prostate cancer. The most critical metric for biomarkers is the negative predictive value (NPV), which is the probability that patients with negative results truly will not benefit from the therapy (126). False negative predictions will prevent the patient from benefitting from treatment. In the cancer types with a very favorable outcome, it is much easier for biomarkers to achieve very high NPV using conventional clinical measures. However, compared to prostate cancer and luminal breast cancer patients, patients with other cancers such as glioblastoma and liver cancer have much worse clinical outcomes. In these cancer types, either there is no effective therapy available, making the biomarker of less value, or genomics biomarkers are not accurate enough for therapies with moderate efficacy. With the rapid development of potent anticancer agents and increasing amounts of clinical genomics data, we foresee that more and better drug response biomarkers in most cancer types will become available for patients and doctors over time.
Recently, an enormous amount of effort has been focused on the development of response biomarkers for ICB (127). While ICB may lead to remarkable clinical responses, for most cancer types, the majority of patients do not respond (10). Multiple factors have been associated with ICB effectiveness, including the degree of cytotoxic T cell infiltration, mutation or neo-antigen load, checkpoint molecule expression, antigen presentation defects, interferon signaling, tumor aneuploidy, some oncogenic signatures, and intestinal microbiota (10, 67, 128–132). However, none of these factors is sufficiently robust to achieve accurate outcome prediction (133). We foresee that computational methods have the potential to identify robust response biomarkers by integrating ICB clinical data with other complementary immuno-oncology data.

**Predicting Therapy Toxicity**

Toxicity is a primary concern for many anticancer drugs. The therapeutic window of a drug is the range of dosages that can treat disease effectively without having intolerable toxicity. Many anticancer drugs have a narrow therapeutic window, with a small difference between the doses for antitumor effects and significant toxicity. However, for certain drugs, the therapeutic window may be very different depending on the patient’s genetic background. For example, 6-mercaptopurine (6-MP) is a drug that treats acute lymphocytic leukemia and chronic myeloid leukemia. The side effects of 6-MP depend on genetic polymorphisms of TPMT, NUDT15, and ITPA (134–136). In this instance, before treatment, genetic tests are necessary to screen patients with specific allele variants, especially the homozygous variants.

Hypothetically, with sufficient training data, genomic biomarkers could be developed to predict the toxicity of a drug in each patient (Figure 1d). A DREAM challenge demonstrated that computational methods could predict cytotoxicity phenotype based on the genetic profiles of lymphoblastoid cell lines (137). Although this study was on cell line models and environmental chemicals (138), it provided a proof-of-concept example that the genotype data together with compound structural attributes might predict individualized toxicity. Currently, there are still no successful data-driven toxicity models that are clinically deployed to predict personalized side effects. With growing data and better computational methods, such models may become feasible in the future.

In addition to predicting personalized drug toxicity, computational models are essential tools in the early stage of drug discovery to screen low-toxicity compounds. With specific toxicity endpoints (e.g., median lethal dose values, tissue-specific toxicity events), quantitative structure–activity relationship (QSAR) models are useful for toxicity prediction through regressions (139, 140). For each chemical, the predictor variables of regression comprise chemical and molecular properties; the response variable could be a toxicity endpoint. Through regression, the QSAR model fits a relationship between chemical structures and toxicity that can predict the activities of new chemicals. A recent study developed a data integration framework named PrOCTOR to predict drug toxicity through the integration of data from drug target expression in tissues, gene network connectivity, chemical structures, and toxicity annotations from clinical trials (141).

Intriguingly, PrOCTOR predicted that many FDA-approved anticancer drugs are unpromising for clinical development due to their cytotoxicity. Therefore, cancer-specific models with distinct schemes from general toxicity prediction might be necessary to predict cancer drug toxicity. Furthermore, such models should consider the more rapid recovery of normal tissue versus tumor tissue after treatment and the ability to mitigate drug toxicity by differences in dose schedule.

It is worth noting that drug toxicity studies are often limited by a lack of sufficient training data. However, there is a wealth of data buried in the archives of the pharmaceutical industry in formats that are difficult to harmonize and analyze. The eTOX project involved collaborations among thirteen pharmaceutical companies, eleven academic institutions, and six small- and medium-sized
enterprises (142). The goal is to build a comprehensive toxicity database and to enable reliable modeling of drug safety endpoints through data sharing. We foresee that the eTOX project will significantly facilitate the development of computational toxicology methods.

Designing Combination Therapies

The emergence of therapeutic resistance together with the frequent incomplete response to primary therapy underscores the importance of effective drug combinations. Currently, most clinically approved combinations, such as dual \textit{BRAF} and \textit{MEK} inhibition in \textit{BRAF}-mutant tumors, are developed from observations in drug-resistant samples or empirical evaluation of drug combinations (143, 144). Alternatively, combinatorial drug screens may identify effective combinations (145). However, the current screening platforms still cannot test all pairwise drug combinations across a broad panel of tumor models to investigate the vast space of potential drug combinations. Thus, data-driven approaches are essential to complement the current experimental methods.

Many data-driven approaches to identify resistance regulators and design combination therapies depend on compound screening data. For example, the molecular characterization of ATP-binding cassette (ABC) transporters across the NCI60 cell line panel identified the transporters that are essential for in vitro drug resistance to certain agents (146). A later analysis of the NCI60 data revealed that the cell-killing effects of thiosemicarbazone significantly correlate with the ABC transporter expression levels (146). This result implicated thiosemicarbazone as a lead compound for targeting multiple chemotherapy resistance (147). Recently, we developed a statistical framework, named CARE, to determine potential regulators of targeted therapy resistance (84). CARE analyzes how drug target genes interact with other genes to affect the drug efficacy in screened cell lines through multivariate regressions. When finding genes regulating lapatinib resistance from both compound screens and clinical data, CARE identified \textit{PRKD3} as the top candidate. Later experiments validated that \textit{PRKD3} inhibition, through either small interfering RNA or compounds, significantly sensitized \textit{HER2} inhibition by lapatinib in \textit{HER2}-positive breast cancer cells.

The examples above focused on finding synergistic drugs that can overcome the resistance to a primary drug. Many studies also aim to discover cotargeting strategies against targets without known inhibitors. For example, a large body of work is identifying drug combinations to mimic \textit{RAS} (e.g., \textit{NRAS}, \textit{KRAS}) inhibition, since direct pharmacological inhibition of \textit{RAS} has been unfeasible. \textit{MEK} is the key downstream component of \textit{RAS} signaling; however, single-agent \textit{MEK} inhibition has been ineffective against tumor cells with activating \textit{RAS} mutations (148). To identify the difference between targeting \textit{MEK} and \textit{RAS}, one study investigated genes whose expression was differentially regulated by eliminating \textit{NRAS} but showed either no change or change in the opposite direction by \textit{MEK} inhibition (149). This study collected gene expression data based on an inducible \textit{NRAS} Q61K-driven mouse model of melanoma, as well as public data sets measuring the transcriptome response of human melanoma cells under various treatments. A statistical model was developed to test the difference of transcriptomic effects between \textit{NRAS} and \textit{MEK} inhibition.

The authors further applied a network modeling approach, named TRAP, to identify the key transcriptional regulators and found \textit{CDK4} as a synergistic target with \textit{MEK} inhibition (149). Combined treatment of \textit{MEK} and \textit{CDK4} inhibitors in mouse models showed significant synergy, which was consistent with earlier studies in cell lines (150).

THE CHALLENGES OF BIG DATA RESEARCH IN CANCER

Given the recent advances in data-driven discoveries catalyzed by the genomics revolution, we may anticipate a significant burst in research productivity. However, big data can also bring significant
challenges instead of breakthroughs. The current data resources in cancer research are far from adequate to answer many important questions about drug response and resistance. Our future efforts should focus on resolving the big data challenges to achieve impactful discoveries.

Inconsistencies Between Data Sets

A common challenge to interpreting the data from clinical studies is that independent cohorts aiming to answer the same question may reach different conclusions. For example, the gene signature of anti-PD1 therapy response identified in one study (151) was not predictive in another study (152). Similarly, many anti-BRAF resistance drivers identified in the literature were not reproducibly found in independent clinical studies (25). From the Gene Expression Omnibus database from the National Center for Biotechnology Information, we collected pairs of human melanoma expression profiles between post-treatment tumors that are resistant to BRAF inhibitors and pretreatment-sensitive tumors. A hierarchical clustering of differential expression profiles between drug-resistant and parental tumors identified 16 distinct clusters with negative correlations between each of the two groups (Supplemental Figure 2). Expression profiles even from the same study appeared in several anticorrelated clusters. One possible interpretation of the inconsistency is that there might be many drug resistance mechanisms, as reflected by the many clusters. Another possibility is that the expression data may reflect passenger alterations instead of drivers. Therefore, it may be premature to draw conclusions from an analysis of a single data cohort without corroborating results from other cohorts, experimental validation, and mechanistic insights.

Another cause of inconsistency arises when data sets from two different technologies measuring the same biological signal lead to different results. For example, the winners from a DREAM challenge in predicting essential genes from shRNA screens failed to predict the top genes from CRISPR screens (106). Further complicating the issue, in high-throughput studies, genomic measurements might correlate with batch effects such as processing platform or date instead of clinical features (153). Therefore, to ensure reliable discoveries, researchers must conduct analyses under robust standards, such as consistent control samples, batch effect removal, and systematic evaluation of independent computational methods, parameters, and cohorts.

Incomplete Clinical Information

In many cancer genomic resources, the lack of treatment information is a particular limitation to data utility. For example, most patients profiled in the TCGA project do not have treatment information. For some cancer types, we may assume that most patients received the standard-of-care therapy. For example, luminal breast cancer patients should get hormone therapies, while HER2+ patients should get trastuzumab treatments. On the other hand, many might have been treated with surgical resection only. However, such treatment information is not explicitly available in TCGA to enable modeling of therapy response and resistance.

Many ongoing efforts are trying to overcome the limitation of available clinical information. For example, an industry collaboration collected about 20,000 patients, for whom both Flatiron electronic health records (EHRs) and Foundation Medicine mutational profiles from next-generation sequencing (NGS) are available (154). The EHR-to-NGS integration linked the longitudinal clinical information with the genomic data and recapitulated findings regarding prognostic biomarkers and therapeutic implications. Another example is the 100,000 Genomes Project that aims to sequence 100,000 whole exomes of diseased and healthy cells from cancer patients and rare disease patients documented in the United Kingdom’s National Health Service (NHS) system. The NHS system provides detailed medical records and health data of all patients for further analysis.
Currently, these genomics resources with detailed clinical information are either proprietary (e.g., EHR-NGS integration; see Reference 154) or in progress (e.g., 100,000 Genomes Project) and thus unavailable for public analysis. However, we foresee that the availability of clinical information should improve in future data cohorts.

The Bottleneck of Data Dimensionality

Recent years have seen many successful examples of big data analytical systems with enormous financial and social impacts, such as the consumer recommendation systems of Amazon, Netflix, and Facebook. However, data science in studying cancer drug effectiveness has only shown limited clinical success. Most clinical studies of anticancer drugs contained profiles of only a small number of patients. For example, several recent studies of ICB released the gene expression profiles of about 30 patients (151, 152, 155, 156), which are not sufficient for selecting response features among all human genes and pathways. In contrast, ImageNet, a data set widely used in computer vision research, contains about 15 million images with detailed hierarchical annotations across 20,000 semantic terms (157). Such a large, well-annotated cohort provided a solid platform to develop deep learning models for image classification, localization, and detection (158). Therefore, there is a significant gap of data dimensionality between cancer biology and other data science fields.

The bottleneck of data dimensionality in cancer research lies in the unique difficulties in sample collection and annotation. ImageNet was able to collect pictures from several internet engines and conduct semantic annotation with the crowdsourcing platform Amazon Mechanical Turk (157). Since image understanding is a natural ability of most people, this crowdsourcing strategy can leverage human power around the world. In contrast, for most cancer types, biopsies through surgical removal of tumors may not happen after metastasis. Even when noninvasive biopsy options are available, genome-scale profiling of cancer samples still incurs a high cost not often reimbursed by medical insurance. Therefore, most data sets of anticancer drug response have small sample sizes (e.g., fewer than 100 patients) compared to the variable dimensionality (e.g., about 20,000 human genes). In the section titled Selecting Variables in High-Dimensional Data, we discussed several algorithmic solutions in analyzing high-dimensional data. However, many limitations in high-dimensional data, such as variable colinearity, may prevent any computational methods from giving robust results. Therefore, other nonalgorithmic solutions are necessary to overcome the bottleneck of data dimensionality in cancer research.

A strategy to overcome the data dimensionality limitation might lie in the data integration. Even though each study may not provide enough information, analyses integrating all studies together can increase the confidence in the results. For example, the eBioPortal platform has integrated 168 cancer genomics data sets with the molecular profiles of 47,135 samples across over 20 cancer types (159). For each gene of interest, this data integration effort enables interactive exploration of molecular alteration patterns and clinical relevance across thousands of samples and neighbor genes in various types of biological networks (160). Similarly, Oncomine integrates 715 cancer genomics data sets across 86,733 samples to enable interactive exploration and analysis of gene functions in cancer (161). Such data integration efforts represent a cost-effective approach to increase sample size through efficient reuse of published resources.

Another strategy to resolve the limitation of clinical data dimensionality is to utilize the large-scale data sets from preclinical models. Especially, the data sets on cancer cell lines can be generated across a much larger number of samples than patient clinical data. Despite some studies questioning whether cell line data could capture clinical relevance (162, 163), several studies demonstrated that the data from compound screens could derive reliable biomarkers to predict clinical response to therapies (84, 164, 165). Moreover, through downsampling analysis, one study demonstrated that
the prediction reliability of biomarkers from preclinical models really benefited from the large sample number (∼1,000 cell lines) of compound screen data (84).

A third solution for breaking the data bottlenecks is through collaborations between industry and academia. There are many large-scale data sets generated in the industry. Even though these resources are primarily proprietary, some companies release their data for scientific research. For example, Novartis released many data sets of pharmacological and genetic screens, such as the CCLE (29), DRIVE (deep RNA interference interrogation of viability effects in cancer) (33), and PDX Encyclopedia (43) cohorts. Recently, the IBM Watson and Broad Institute launched a five-year, $50 million initiative to collect genomics data from about 10,000 drug-resistant samples. Similarly, collaborations among multiple research institutions can also provide large-scale clinical genomics data sets. For example, the GENIE project is an international data sharing initiative among eight institutions that released mutation profiles for more than 500 genes and a minimal set of clinical information for almost 30,000 cancer patients until the end of 2017 (24).

Lastly, there are also several efforts in creating new resources from published data sets (166–168). Even though they may not focus on anticancer drug efficacy, some of them provide good examples of public data reuse to answer specific questions. For example, the CREEDS (crowd-extracted expression of differential signatures) project collected thousands of drug and gene perturbation signatures using the crowdsourcing approach through an online Coursera course with about 70 participants across 25 countries (168). Such crowdsourcing strategies devised by experts may enable efficient reuse of public data to create larger data sets for cancer research.

CONCLUSION

In this review, we summarized the literature on high-throughput technologies and data-driven approaches that model the efficacy of anticancer drugs. Despite the abundant literature and a few successful clinical applications, there are still many unsolved problems and new challenges. Our review primarily focused on small molecule or antibody drugs. However, there are many other types of anticancer therapies, such as radiotherapy, cell therapy (169, 170), personalized vaccines (171, 172), nanoparticles (173), and fecal transplantation (17, 69, 70). Genomic profiling efforts for these conventional and emerging treatment modalities may bring new challenges and opportunities to data science.

The success of precision cancer medicine hinges on using data science to better characterize the interactions between the tumor microenvironment, host immunity, and the ecosystem. Meanwhile, the translation from analytic results to prognosis and treatment regimens in the clinics requires the collaboration of the whole scientific community, including data scientists, molecular biologists, and clinical oncologists. With the increasing availability of big data resources and computational methods, we envision that big data approaches will significantly contribute to the future development of precision cancer medicine.

DISCLOSURE STATEMENT

W.R.S. is a former employee and shareholder of Novartis Pharmaceuticals and a patent holder of EGFR mutation testing. X.S.L. is a co-founder and shareholder of GV20 Oncotherapy.

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Errata
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